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EXAMINER

UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 02/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/016,248

Applicant(s)

ALSOBROOK ET AL

Examiner

Susan Ungar

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 20 August 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 50-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 50-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/3/2002, 3/12/2003
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

1. The Response/Election filed August 20, 2004 in response to the Office Action of July 28, 2004 is acknowledged and has been entered. Claims 1-49 have been canceled in response to the restriction requirement and new claims 50-58 have been added. Claims 50-58 are currently under prosecution.
2. The response to the restriction requirement of July 28, 2004 has been received. Applicant has canceled the pending claims and added claims 50-58 drawn to restriction group 23-44, that is Claims 5-14, 39, 42 drawn specifically to SEQ ID NO:1 encoding SEQ ID NO:2, a vector and a host cell.

Applicant traverses the restriction requirement and states that both SEQ ID NOs: 1 and 3 are variants of Human Cub and Sushi domain containing proteins. Since both sequences defined by these identification numbers belong to the same gene family, the search requirement will necessarily encompass all the variants of the gene. It appears that Applicant is suggesting that the search of both inventions would not impose a serious burden on the examiner. This is not found persuasive because the literature search, particularly relevant in this art, is not coextensive and different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). In particular, non-dated alterations have been made to Dr. Boldog's name.

Specification

4. The specification on page 1 should be amended to reflect the status of the parent application serial numbers.

Further, the claim to priority to the provisional applications is improper, the proper form is as follows:

“This application claims benefit to provision application *****, filed **, now abandoned.

Appropriate correction is required.

5. The specification is objected to because it contains embedded hyperlinks and/or other form of browser-executable code, for example on page 13, page 28. Applicant is required to identify and delete all of the embedded hyperlinks and/or other form of browser-executable code used in the specification. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC §101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 50-58 are rejected under 35 U.S.C. 101 because the claimed invention lacks specific, substantial utility and a well established utility.

The disclosed utilities for the NOVX nucleic acid and polypeptide, which include NOV1a, the nucleic acid of SEQ ID NO:1 (which encodes the novel polypeptide SEQ ID NO:2) include use as a therapeutic in the manufacture of a medicament for treating the laundry list of diseases recited on pages 2 and 3 of the specification. Further, the polypeptides of the invention can be used as immunogens to produce antibodies specific for the invention and as vaccines as well as for the screening for potential agonist and

antagonist compounds (p. 4, lines 20-25) and, a cDNA encoding NOVX may be useful in gene therapy, for the screening for modulators of disorders or syndromes (p. 4, lines 30-35), in a method for determining the presence of or predisposition to a disease associated with altered levels of NOVX polypeptide, nucleic acids or both (p. 5, lines 15-20), a NOVX nucleic acid or polypeptide can be used in a method of treating or preventing a pathological condition associated with a disorder (p. 5, lines 26-30), in disorders characterized by increased levels or biological activity of NOVX, therapeutics that antagonize activity may be administered, in disorders that are characterized by decreased levels of biological activity may be treated with agonists that increase activity, increased or decreased activity can easily be detected by quantifying RNA or protein from a patients tissue (pages 199-200). The specification summarizes the exemplification and states that (1) cell lines studies disclosed overexpression of the assayed polynucleotide in a single brain cancer cell line, given this information, Applicant hypothesizes that modulation of gene expression **might** (emphasis added) be of benefit in the treatment of brain cancer, (2) moderate levels of expression were found in a number of metabolic tissues including adrenal, pituitary, heart and fetal skeletal muscle, given this information, Applicant hypothesizes that this gene product **may be** (emphasis added) important for pathogenesis, diagnosis and/or treatment of metabolic disease, including obesity and given the higher levels of expression of this gene in fetal muscle as compared to adult muscle, Applicant hypothesizes that the gene product **could be** (emphasis added) used to restore muscle mass or function, (3) the probed genes represent novel proteins containing CUB and sushi domains, they are highly brain preferential and since at least one brain-specific protein containing CUB and sushi domains has been linked to seizures, the specification states that therefore this protein is therefore a drug target for the treatment of epilepsy or any seizure disorder. It is noted

that it does not appear that the specification is referring to the protein encoded by SEQ ID NO:1, but rather to the known brain-specific protein disclosed, (4) the specification discloses that there are many proteins with multiple sushi and CUB domains, (5) gene overexpression was detected in colon cancer samples, liver cancer, prostate cancer, lung cancer, kidney cancer, bladder cancer and gene underexpression was detected in kidney cancer, liver cancer given this information, the specification hypothesizes that therapeutic modulation of this gene **might be** of benefit in the treatment of these cancer types (pages 231-232). The specification teaches that the probe used in the expression assays summarized above is not specific to SEQ ID NO:1 wherein the specification teaches that Expression of gene CG50377-01 (SEQ ID NO:1) and variant CG50377-02 SEQ ID NO:3 were assessed using the primer-probe sets Ag2420, Ag169, Ag65 and Ag575 (see paragraph 0670 of published application). It is noted that given the above, it is not possible to determine whether the overexpression or underexpression of the gene disclosed on pages 231-232 of the specification is drawn to SEQ ID NO:1 or SEQ ID NO:3 or both. This is clearly a critical issue given that gene over expression was detected in kidney cancer and liver cancer and that gene under expression was also detected in the same cancer types.

In particular as drawn to NOV1a, SEQ ID NO:1, the specification teaches that NOV1a is homologous to a Cub and Sushi Domain-containing-like family of proteins and thus is useful in therapeutic and diagnostic applications implicated in cancer, obesity, inflammation, hypertension, neurological diseases, neuropsychiatric diseases, small stature, obesity, diabetes, hyperlipidemia and other diseases, disorders and conditions of the like (p. 7, lines 8-13). NOV1a has 99% identity to 257 of 259 bases of a Homo sapiens mRNA (p. 12, lines 2-6). The encoded polypeptide appears to have a signal peptide, it likely to be localized outside the cell, but may also be localized in the

lysosome luman, the microbody or the endoplasmic reticulum (p. 13). Further, SEQ ID NO:1 has 29% identity, 145 of 489 amino acids, and is 44% similarity, 216 of 489 amino acids, to Homo sapiens Complement Receptor 1 (p. 14) and is expressed at least in the adrenal gland and the pituitary gland as determined by comparison to various databases and literature sources (p. 14). Further CUB domains are important protein interaction domains found in a variety of growth factors and other proteins. The specification therefore hypothesizes that this protein **may** (emphasis added) mediate cell-cell contact, growth or other important cellular processes (p. 29, lines 1-5).

However, neither the specification nor any art of record teaches a specific utility for SEQ ID NO:1 or the polypeptide encoded thereby they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Although the specification reveals the overexpression and underexpression of a gene using probes that hybridize to both SEQ ID NO:1 and SEQ ID NO:3, even in the same cancer types as set forth above, it is not possible to determine from the information in the specification which or whether both or only one of the sequences is overexpressed or underexpressed and if only one, which one is overexpressed or underexpressed and thus associated with any particular cancer. Thus additional work must be done to establish which of the genes is in fact overexpressed or underexpressed because it is not possible to determine from the specification if SEQ ID NO:1 is in fact associated with any disease or condition and whether or not it would be useful for the treatment or diagnosis of any disease or condition and thus the claimed invention does not have substantial utility. Further, the specification makes liberal use of terms and phrases such as “may”, “might be”, “could be”, “might”, “may be”. Clearly additional work must be done in order to determine which of these hypothesized functions actually are resident in SEQ ID NO:1 and the specification does not have substantial utility.

Since the claimed invention does not have substantial utility, the polypeptide encoded by the polynucleotide does not have substantial utility.

Further, the claimed invention does not to have a specific utility because it appears that the utility of the claimed invention is based upon the presence of the CUB and sushi domains. However, the specification makes clear that many proteins, with different functions, contain CUB and sushi domains and thus these domains do not provide a specific utility because the utility is shared by many other proteins. In addition, the suggested uses drawn to encoded protein such as production of antibodies and screening for agonists and antagonists are not specific to the encoded protein because these are functions common to all polypeptides.

Further, the utility of the claims invention is based on the 29% identity, 44% similarity of the claimed invention to Complement Receptor perhaps inferring that the claimed invention has a well established utility. However, this identity/similarity does not establish either a well established or specific utility because although there is 29% identity, 44% similarity, there is also a 71% lack of identity, 56% lack of similarity between the putative encoded protein and Complement Receptor and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence

where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with a 71% lack of identity, 56% lack of similarity, to Complement Receptor, the function of the polypeptide encoded by SEQ ID NO:1 could not be predicted, based on sequence similarity with Complement Receptor, nor would it be expected to be the same as that Complement Receptor. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity

wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important

features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by US Pub 20030105000 which specifically teaches on page 73 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity or similarity alone can not be used to predict the function of a protein. Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al, Scott et al, US Pub US Pub 20030105000 but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 71% lack of identity, 56% lack of similarity, to Complement Receptor the function of the polypeptide encoded by SEQ ID NO:1 could not be predicted, based on sequence similarity with Complement Receptor nor would it be expected to be the same as that of Complement Receptor. Further work would need to be done in order to establish a functional use for the claimed invention and the invention does not have substantial utility. Further, even if the claimed invention encoded a Complement Receptor-like protein, the polypeptide does not have a well-established utility because neither the specification nor any art of record teaches what the novel polynucleotide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate functional use for the claimed invention and thus the claimed

nucleic acid molecules has none of specific, substantial or well established utility and the encoded polypeptide also has none of specific, substantial or well established utility. Because the claimed invention is not supported by a specific asserted utility, a substantial utility, a well established utility for the reasons set forth, credibility of any utility cannot be assessed.

8. Claims 50-58 are rejected under 35 USC 101 because the disclosed invention is inoperative and therefore lacks utility.

Claims 50-58 are inoperative because claim 50 is drawn to an isolated nucleic acid molecule encoding an amino acid selected from the group consisting of (a), (b) and (c), however, although (a) and (b) are recite amino acid sequences, (c) is not an amino acid sequence, but rather it is a nucleic acid molecule. The rejection may be obviated by amending the claim, for example to read “An isolated nucleic acid molecule comprising(a).....; (b).....; or a nucleic acid molecule comprising the complement thereof”.

Claims 53 is inoperative because it is drawn to the nucleic acid molecule of claim 50, that is an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence, wherein said nucleic acid molecule hybridizes under stringent conditions to a nucleotide sequence of SEQ ID NO:1. In particular the claim is inoperative because the complete complement of SEQ ID NO:1 could not encode SEQ ID NO:2 because each of the residues would be the complement of a residue of SEQ ID NO:1.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

10. Claims 50-58 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a specific asserted utility, a substantial utility, a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

11. If applicant were able to overcome the rejection under 35 USC 112, first paragraph, Claims 50-51, 53-58 would still be rejected under 35 USC 112, first paragraph because the specification while enabling for an isolated nucleic acid comprising SEQ ID NO:1, does not reasonably provide enablement for a nucleic acid molecule comprising (1) a nucleic acid that encodes SEQ ID NO:2 (2) encodes an amino acid sequence of SEQ ID NO:2, (3) a nucleic acid comprising the complement thereof, (4) a nucleic acid that differs by a single nucleotide from a nucleic acid sequence of SEQ ID NO:1, (5) a nucleic acid molecule that hybridizes under stringent conditions to a nucleotide, a complement of said nucleotide sequence, (6) a cell comprising the vector of claim 54, (7) a pharmaceutical composition comprising a nucleic acid molecule according to claim 50. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification teaches that probes that hybridize to both SEQ ID NOS 1 and 3 demonstrate that one or both of these sequences are overexpressed in a variety of cancers (pages 217-227) and teaches that complementarity refers to Watson-Crick or

Hoogsteen base pairing between nucleotide units of a nucleic acid molecule (p. 137, lines 20-29), and teaches that stringent hybridization conditions refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence but to no other sequences (p. 141, lines 15-25), and teaches pharmaceutical compositions for the treatment of a variety of diseases including cancer (pages 2-3 of the specification).

One cannot extrapolate the teaching of the specification to the scope of the claims because

(1) the claims are drawn to nucleic acid molecules that encode SEQ ID NO:2, this means any nucleic acid that encodes SEQ ID NO:2, regardless of its identity with SEQ ID NO:1, however, neither the specification nor the art of record provide any nexus between any cancer and any sequence encoding SEQ ID NO:2 other than SEQ ID NO:1. In particular, one cannot extrapolate the claimed invention to a whole universe of degenerate sequences of SEQ ID NO:1, the overexpression of which is not predictable since it cannot be predicted that the claimed degenerate sequences would have the same promoter or enhancers as the sequence comprising SEQ ID NO:1. Further, there is no guidance of which degenerate sequences of SEQ ID NO:1 would be overexpressed in any type of cancer as compared to normal tissue. Since one cannot predict whether the claimed degenerate sequences would be overexpressed in lung cancer tissue as compared to normal tissue, one would not know how to use the claimed invention.

It is noted for Applicant's convenience that the instant rejection could be obviated by amending claim 50, for example to recite "An isolated nucleic acid molecule comprising SEQ ID NO:1.

(2)-(5) the claims are drawn to polynucleotide comprising: (2) a polynucleotide that encodes an amino acid sequence of SEQ ID NO:2, this means a polynucleotide

which encodes a fragment of a SEQ ID NO:2 within a sequence that has neither the structure nor the function of SEQ ID NO:2; (3) a nucleic acid comprising the complement thereof, this means any size nucleic acid that pairs with any portion of SEQ ID NO:1; (4) a nucleic acid that differs by a single nucleotide from a nucleic acid sequence of SEQ ID NO:1, this means a polynucleotide fragment within a sequence that has neither the structure nor the function of SEQ ID NO: 1; (5) a nucleic acid molecule that hybridizes under stringent conditions to a complement of said nucleotide sequence, this means any probe, primer or oligonucleotide that will hybridize to its target sequence.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that the claimed limitations are drawn to a whole universe of nucleic acid molecules that comprise fragments of SEQ ID NO:1 or encode fragments of SEQ ID NO:2 within a larger sequence. It is clear, given the above drawn to both complementarity and stringent conditions, that the terms are drawn to not only complete complements, but also to species that are partial complements of SEQ ID NO:1 or polynucleotides encoding SEQ ID NO:2 as well as nucleic acid molecules comprising fragments of SEQ ID NO:1 and encoding fragments of SEQ ID NO:2 within other sequences. Although the specification teaches that the polynucleotides of the invention can be used for diagnosis and treatment of a variety of diseases, there is no teaching of how to use the claimed inventions as currently constituted for any of the purposes hypothesized in the specification . In particular, even if a function for the claimed invention were to be known, as set forth above, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions

of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon

analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging

cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by US Pub 20030105000 which specifically teaches on page 73 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity or similarity alone can not be used to predict the function of a protein. Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al, Scott et al, US Pub US Pub 20030105000 but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, it would not be expected and could not be predicted that any of the claimed species would function as contemplated in the specification. Finally, the specification does not provide teachings or working examples which would provide sufficient guidance to allow one of skill in the art to use the multitude of polynucleotide sequences encompassed by the scope of the claims. Clearly, it would be expected by one of ordinary skill in the art that a substantial number of the polynucleotides comprising fragments of SEQ ID NO:1, encoding polypeptides comprising fragments of SEQ ID NO:2, hybridizing or complementary polynucleotides encompassed by the claims **would not** encode proteins that share either structural or functional properties with SEQ ID NO:2. Further, the specification does not provide either guidance on or exemplification of how to use the multitude of polynucleotides

encompassed by the claims that do not encode proteins that share either structural or functional properties with SEQ ID NO:2.

It is noted for Applicant's convenience that the rejection may be obviated by amending claim 50 to recite, for example, "An isolated nucleic acid molecule comprising SEQ ID NO:1 or the complete complement thereof".

(6) In particular, Claim 56 is drawn to a cell comprising said vector, this means not only an isolated host cell but also a cell within a human patient wherein the patient is being treated with gene therapy as contemplated in the specification on page 4, lines 22-30.

One cannot extrapolate the teaching of the specification to the scope of the claims because it was well known in the art at the time the invention was made that the status of the field of gene therapy in humans was unpredictable in regard to obtaining therapeutic levels of transcription in a host subject. Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. In addition, Marshall (Science, 1995, 269:1050-1055) teaches that there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col 1) and that "difficulties in getting genes transferred efficiently to target cells - an getting them expressed - remain a nagging problem for the entire field" (p. 1054, col 3). James Wilson, one skilled in the art stated that "{t}he actual vectors- how we're going to practice our trade - haven't been discovered yet" (p. 1055, col 2). Culver et al

(TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). Miller et al (FASEB J., 1995, 9:190-199) also reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy there will have to be advances, targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). Finally, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, the issues raised by the Orkin report, although being addressed, have not been resolved. It is noted that the instant rejection may be overcome by amending claim 56, for example, to recite "An isolated cell".

(7) In particular, Claims 57-58 are drawn to a pharmaceutical composition comprising a nucleic acid molecule according to claim 50 and a kit comprising said pharmaceutical composition.

One cannot extrapolate the teaching of the specification to the scope of the claims because inherent in a pharmaceutical composition is the *in vivo* use of the composition for the treatment of disease. In particular, the specification teaches the overexpression or underexpression (p. 232, lines 27-42) in a variety of cancer types, of a gene that hybridizes to a probe known to bind to two different sequences, contemplates the treatment of cancer and a variety of other diseases. However, although the specification contains numerous lists of diseases to be treated, in the interests of compact prosecution, only the contemplated treatment of cancer will be discussed here. It is clear that this discussion is relevant to the other listed diseases as well. In particular as drawn to the cancer arts, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the nucleic acid will function as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common

solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the nucleic acid will function as claimed. In addition, Hartwell et al (Science, 1997, 278:64-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). In addition, anti-tumor agents or imaging agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before

producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the antibody. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established.

Further, it is noted that the specification specifically contemplates gene therapy with the claimed nucleic acid molecules. However, as set forth above, it was well known in the art at the time the invention was made that the status of the field of gene therapy in humans was unpredictable in regard to obtaining therapeutic levels of transcription in a host subject. Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. In addition, Marshall (Science, 1995, 269:1050-1055) teaches that there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col 1) and that "difficulties in getting genes transferred efficiently to target cells - an getting them expressed - remain a nagging problem for the entire field" (p. 1054, col 3). James Wilson, one skilled in the art stated that "{t}he actual vectors- how we're going to practice our trade - haven't been discovered yet" (p. 1055, col 2). Culver et al (TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for

delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). Miller et al (FASEB J., 1995, 9:190-199) also reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy there will have to be advances, targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). Finally, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, the issues raised by the Orkin report, although being addressed, have not been resolved. It is noted for Applicant's convenience that the rejection may be obviated by amending claim 57 and 58, for example to recite "A composition" and deleting reference to a pharmaceutical composition.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed, that is as contemplated and claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

12. Claims 50-51, 53-58 are rejected under 35 USC 112, first paragraph because the instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are drawn to isolated nucleic acid molecules comprising a nucleic acid sequence encoding **an** (emphasis added) amino acid sequence of SEQ ID NO:2, an isolated nucleic acid molecule comprising the complement thereof, wherein the nucleic acid molecule differs by a single nucleotide from **a** (emphasis added) nucleic acid sequence of SEQ ID NO:1, wherein said nucleic acid molecule hybridizes under stringent conditions to **a** (emphasis added) nucleotide sequence of SEQ ID NO:1 or a complement thereof, a vector comprising said sequence, a cell comprising said vector a composition and kit comprising said sequence. Given the claim language as currently constituted, it is clear that the claims are drawn to molecules comprising fragments of SEQ ID NO:1 as well as molecules encoding polypeptides comprising fragments of encoded SEQ ID NO:2.

The specification discloses an isolated cDNA sequence, SEQ ID NO: 1, which encodes a predictive polypeptide sequence, SEQ ID NO. 2. The claims, as written, encompass polynucleotides which vary substantially in length and also in nucleotide

composition. The broadly claimed genus additionally encompasses genes encoding SEQ ID NO:2 as well as genes incorporating only portions of the disclosed sequence.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and

untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, encoding SEQ ID NO:2 or genes comprising fragments of SEQ ID NO: 1.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 50, 53, 57-58 are rejected under 35 U.S.C. § 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93).

It is noted that the preamble recitation of pharmaceutical composition is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which is the claimed nucleic acid molecule and a carrier.

It is noted that, for examination purposes, that encoding “an amino acid sequence of SEQ ID NO:2” is understood to mean encoding any sequence of SEQ ID NO:2 which reads on coding for two amino acids of the sequence.

The claims are drawn to an isolated polynucleotide comprising a polynucleotide sequence which codes for an amino acid sequence of SEQ ID NO:2, the complement of an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide, wherein said nucleic acid molecule hybridizes under stringent conditions to a nucleotide sequence of SEQ ID NO:1, a composition comprising said nucleic acid molecule and a kit comprising, in one or more containers said composition.

The Boehringer Mannheim teaches a kit comprising a composition comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924) a subset of which will be a complement of the claimed polynucleotides, will encode two amino acids of SEQ ID NO:2, will hybridize under stringent conditions. All of the limitations of the claims are met.

15. Claim 50 is rejected under 35 U.S.C. § 102(b) as being anticipated by Carninci et al (Meth. Enzymol., 1999, 303:19-44).

It is noted that, for examination purposes that an isolated nucleic acid molecule comprising a nucleic acid sequence encoding “an amino acid sequence of SEQ ID NO:2” is understood to mean any nucleic acid encoding any sequence of SEQ ID NO:2 of two or more amino.

The claim is drawn to an isolated nucleic acid molecule encoding an amino acid sequence comprising an amino acid sequence of SEQ ID NO:2 (claim 50).

Carninci et al teach a nucleic acid sequence which encodes numerous sequences of SEQ ID NO:2 (see us-10-016-248-2.rst, result 3).

16. Claims 50-51, 53-55, 57 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillier et al (AI928999), Genbank Sequence Database (Accession AI928999), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available August 23, 1999.

It is noted that the preamble recitation of pharmaceutical composition is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which is the claimed nucleic acid molecule and a carrier.

It is noted that, for examination purposes because the specification does not define complementarity in a limiting fashion, that the “complement” thereof is assumed to be a partial complement. Further, it is noted that claim 53 is drawn to a nucleic acid molecule that hybridizes under stringent conditions to “a” nucleotide sequence of SEQ ID NO:1, thus it is clear from the claim language that the claims are not drawn to the complete complement of SEQ ID NO:1.

The claims are drawn to an isolated nucleic acid molecule comprising the complement of a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:2 (claim 50), wherein said nucleic acid molecule differs by a single nucleotide from a nucleic acid sequence of SEQ ID NO:1 (claim 51), wherein said nucleic acid molecule hybridizes under stringent conditions to a nucleotide sequence or SEQ ID NO:1 or a complement of said sequence (claim 53), vector comprising said nucleic acid (claim 54), comprising a promoter operably linked to said nucleic acid molecule (claim 55), a composition comprising said nucleic acid (claim 57).

Hillier et al teach a nucleic acid molecule that is 99.8% identical to 4.3% of SEQ ID NO:1, wherein one would immediately envision the complete complement thereof,

wherein said molecule differs by a single nucleotide from a nucleic acid sequence of SEQ ID NO:1, that is nucleotides 5560-6010 of SEQ ID NO:1, wherein said nucleic acid will hybridize under stringent conditions to the complete complement of a nucleotide sequence of SEQ ID NO:1, nucleotides 5560-6010, wherein said sequence is inserted into a pBluescript vector and is shipped in composition form in a pharmaceutically acceptable carrier (see us-10-016-248-1.rst) and thus the composition comprises said nucleic acid molecule.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

18. Claims 50, 54-58 are rejected under 35 U.S.C. § 103 as being unpatentable over Carninci et al, *Supra* and Hillier et al, *Supra* in view of US Patent No. 4,889,806 and Sambrook et al (Molecular Cloning, a Laboratory Manual, 1989, Cold Spring Harbor Press, p. 16.3-4).

It is noted that the preamble recitation of pharmaceutical composition is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which is the claimed nucleic acid molecule and a carrier.

It is noted that, for examination purposes that an isolated nucleic acid molecule comprising a nucleic acid sequence encoding “an amino acid sequence of SEQ ID NO:2” is understood to mean any nucleic acid encoding any sequence of SEQ ID NO:2 of two or more amino.

The claims are drawn to an isolated nucleic acid molecule encoding an amino acid sequence comprising an amino acid sequence of SEQID NO:2 (claim 50), a vector comprising said nucleic acid (claim 54), comprising a promoter operably linked to said nucleic acid molecule (claim 55), a cell comprising said vector (claim 56), a composition comprising said nucleic acid (claim 57), a kit comprising said composition (claim 58).

Carninci et al teach as set forth above, but do not teach the nucleic acid molecule in a vector comprising a promoter operably linked to said nucleic acid, a cell comprising said vector, a composition comprising said nucleic acid in a pharmaceutically acceptable carrier, a kit comprising said composition.

Hillier et al teach as set forth above, but do not teach the nucleic acid vector inserted into a cell or a kit comprising said composition

US Patent No. 4,889,806 teaches vectors, or plasmids defined as Yeast Artificial Chromosome (YAC) vectors (col 3, lines 42-44) and teach that with the advent of recombinant DNA and molecular cloning technology it is now conventional to transfer genetic information into any source using small plasmids constructed in vitro and then transferred into host cells and clonally propagated and that most DNA cloning systems have a capacity for only small segments of exogenous DNA and are well suited to the analysis and manipulation of typical genes and that the YAC cloning system allows the cloning of large segments of exogenous DNA (col 1, lines 18-50) and have significant utility in the analysis of megabase-pair regions of DNA which lead to mapping of large regions of DNA and the cloning of candidate genes involved in disease.

Sambrook et al teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the nucleic acid molecule of Carninci et al with the methods of US Patent No. 4,889,806 to produce vectors for the expression of the nucleotides and to combine the vector Hillier et al with the methods of US Patent No. 4,889,806 to insert said vectors into host cells because Sambrook et al and US Patent No. 4,889,806 teach that cDNA is conventionally expressed using a vector system. One of ordinary skill in the art would have been motivated to combine the nucleic acid

molecule of Carninci et al and the vector of Hiller et al and the methods of US Patent No. 4,889,806 because the nucleic acid molecule of Carninci et al and the nucleic acid molecule inserted into vector of Hillier et al are novel uncharacterized polynucleotides encoding uncharacterized proteins and because Sambrook et al teach that expression of cloned proteins have been used to (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins which would be useful in characterizing the protein and one would be motivated to use the YAC cloning system because US Patent No. 4,889,806 specifically teaches that the system has significant utility in the analysis of megabase-pair regions of DNA which would lead to the cloning of candidate genes potentially involved in mammalian functions. Further, it would have been *prima facie* obvious and one would have been motivated to make a composition comprising the nucleic acid of Carninci et al inserted into a vector with a pharmaceutically acceptable carrier because Hillier et al teach the conventional production of vectors in composition form.

Finally, it would have been *prima facie* obvious, and one would have been motivated, at the time the invention was made to make a kit comprising said polynucleotides/vectors for characterization testing because standard kits enhance the probability of the reproducibility and efficiency of the characterization process.

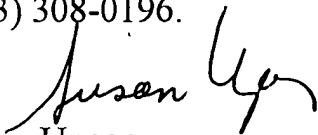
19. No claims allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703)

305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 571-0787. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read "Susan Ungar", with a stylized flourish at the end.

Susan Ungar
Primary Patent Examiner
October 29, 2004